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Risk of gastrointestinal complications associated to NSAIDs, low-dose aspirin and their combinations: Results of a pharmacovigilance reporting system

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ABSTRACT

Gastrointestinal (GI) complications are one of the most limiting cause of use of NSAIDs. Beyond others well defined factors, history of peptic ulcer, older age, *Helicobacter pylori* infection and use of gastrotoxic drugs may affect their GI safety profile. In particular, the risk of GI complications associated to the use of antiplatelet drugs, especially low-dose acetylsalicylic acid (LDA) should deserve much attention. However, only few studies have focused on the effect of combination LDA/NSAIDs on the GI tract compared with the monotherapy and much less studies assessed this effect with multiple NSAIDs use. We aimed to characterize the GI safety profile of NSAIDs and LDA as monotherapy or their combinations in real-life conditions by analysing spontaneous adverse drug reactions (ADRs) reporting system in a Southern Italy. We used the case/non-case method in the Italian Pharmacovigilance Network (RNF). Cases were reports of GI events in the RNF between January 2007 and December 2011. Non-cases were all other reports during the same period. The association between NSAID and suspected GI ADRs was calculated using the reporting odds ratio (ROR) with 95% confidence intervals as a measure of disproportionality while adjusting for age, and concomitant use of antineoplastic agents or drugs for cardiovascular diseases. Sub-analysis were performed within the NSAID class. Among the 2816 adverse drug reactions recorded, we identified 374 (13.3%) cases of GI complications. Upper GI complications were the most frequently reported type of events. The highest associations were found for the combined use of NSAIDs and/or LDA, whilst the lowest associations were for their respective monotherapy. Looking at individual NSAIDs the highest association with GI events was observed for ketorolac exposure followed by nimesulide, diclofenac, aspirin, ketoprofen, and ibuprofen. This study highlights the primary role of the national spontaneous reporting system to bring out potential signals, such as the inappropriate drug use pattern, which however, have to be furtherly studied in-depth with ad hoc population-based studies.

1. Introduction

Despite the heterogeneity in terms of chemical structure and clinical profile, non-steroidal anti-inflammatory drugs (NSAIDs) share the same pharmacological action and therapeutic effects; in particular, NSAIDs serve as efficacious pharmacological treatment of inflammatory and painful conditions, both acute and chronic. These therapeutic effects, taken together with the spread of chronic

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rheumatic diseases and the increased life expectancy, make NSAIDs one of the most prescribed drug classes worldwide [1]. On the other hand, gastrointestinal (GI) complications, ranging from mild to severe dyspeptic symptoms, development of gastric or duodenal ulceration, hemorrhage or perforation and other events potentially leading to hospitalization or death, represent one of the most limiting cause of use of these drugs [1]. In particular, these events are mainly related to the inhibition of the cyclooxygenase (COX) enzymes, of which two isoforms are well recognized, namely: COX-1, which is constitutively expressed in many cells and tissues and mediates gastroprotective prostaglandin production, and COX-2, which is selectively induced by proinflammatory cytokines at the site of inflammation [1]. The use of NSAIDs has been associated with a 3- to 5-fold increase in the risk of gastrointestinal complications [2] and the mortality related to these events ranges from 5 to 12% [3]. However, the gastrotoxic effects related with NSAIDs use differs among this drug group; first of all, named first-generation NSAIDs that acts blocking both COX-1 and COX-2 isoforms is associated with higher risk of GI complications than the second-generation agents, the COX-2 selective inhibitors [1]. However, although these agents have been developed as preventive strategy of gastrointestinal adverse effects, several studies have demonstrated that the risk of such complications is not completely eliminated, albeit it is lower compared to non-selective NSAIDs [2]. The distinction in first- and second-generation NSAIDs is not the only discerning of gastrointestinal toxicity, but, taking into account many findings, the risk varies according to the individual molecule of this drug group [2,4–9]; this variability is partly explained by the different acidity of molecules, plasma half-life, COX-1/COX-2 selectivity, commercialized doses and formulations [1,2,10], but other factors may affect the GI safety profile. Several risk factors for GI complication in people treated with NSAIDs have been identified to date, namely: history of peptic ulcer, older age (>60 years), *Helicobacter pylori* infection and use of gastrotoxic drugs [10]. As far as the latter risk factor, while gastrotoxicity of corticosteroids, anticoagulants, selective serotonin reuptake inhibitors (SSRIs), calcium antagonists and other antihypertensive drugs, when used in combination with NSAIDs is well known, the risk of GI complications associated to the use of antiplatelet drugs, and among these, especially low-dose acetylsalicylic acid (LDA) should deserve much attention [10]. LDA (75–160 mg/day) is now widely used for both primary and secondary prevention of cardiovascular and cerebrovascular diseases although, in the primary prevention its risk/benefit ratio is still under discussion [11,12]. LDA, even at very low dose, is associated with a relative risk of GI events ranged from 1.6 to 4.0 compared with no use [13]. As a consequence it would be expected that the combination of NSAIDs with LDA, both most frequently prescribed drugs especially in the elderly patients, which are themselves at higher risk, further increases the risk of GI complications. However, only few studies have focused on the effect of combination LDA/NSAIDs on the GI tract [13–17] compared with the monotherapy and much less studies assessed this effect with multiple NSAIDs use. In this scenario, we aimed to characterize the GI safety profile of NSAIDs (including COX-2 inhibitors) and LDA as monotherapy or their combinations in real-life conditions by analysing spontaneous adverse drug reactions (ADRs) reporting system in Campania region (Southern Italy) during the period from 2007 to 2011. Moreover, since the evaluation of the safety profile differences between these compounds based on information inferred from a "real world" population may allow for better tailoring of NSAID therapy to individual patient features, we attempted to define the GI safety of individual NSAIDs.

2. Methods

2.1. Data source

Italian Pharmacovigilance Network (Rete Nazionale di Farmacovigilanza, RNF) is a nationwide spontaneous reporting database activated in 2001 by Italian Medicine Agency (Agenzia Italiana del Farmaco, AIFA) to collect all ADRs spontaneously reported by health care professionals as well as citizens. According to legislative decree 95/2003, this Network has been implemented by the institution of Regional Centres of Pharmacovigilance (Centro Regionale di Farmacovigilanza, CRFV) in order to improve the knowledge on the importance of the ADRs and to monitor the efficiency of the system. Campania is one of the first regions that institutionalized a Regional Centre of Pharmacovigilance and actually is the most active CRFV contributing with the spontaneous reporting ADRs to the RNF [18,19]. The network has been previously described as a valid system for safety surveillance [20–22].

2.2. Selection of cases and non-cases

For this study, we used all the reports of suspected ADRs occurring in people >18 year olds, as registered in RNF coming from Campania region during the period January 2007 until December 2011. Each suspected ADR report includes information on patient demographics (e.g., age, gender, region), report source, ADR outcome, date of onset of the suspected ADR, seriousness; preferred terms of MedDRA (Medical Dictionary for Regulatory Activities), and unstructured narrative of each event, drug/vaccine information for as many medications as reported for each event (active ingredient name, trade name, Anatomical Therapeutic Classification code, ATC), therapy start and end dates, and indications of use, whenever available. Duplicate reports are automatically detected from the system [18,21].

Associations between specific drugs and GI ADRs were analyzed using the case/non case approach [23,24], the mostly used method for signal detection, introduced in 1991 in a study with WHO data on serum sickness to cefaclor [25]. Cases of GI events were defined as reports of suspected ADRs in which at least one of the following preferred terms was indicated: gastric and/or duodenal ulceration, gastrointestinal bleeding, oesophagitis, gastritis and duodenitis erosive and non-erosive.

GI cases were manually validated by gastroenterologists, in order to reduce bias for event misclassification. Actually, all cases of heartburn as refereed by the patient without any other symptom/sign of GI, which are suggestive of GI event but are not sufficient by themselves for the diagnosis, were considered as GI cases only in association with other more specific symptoms/signs, otherwise were excluded from the analysis. Non-cases were all non-GI suspected ADR reports.

2.3. Definition of drug of interest

Different groups of exposure of interest were considered: (1) *Nonsteroidal anti-inflammatory drugs* for systemic use (NSAIDs, ATC: M01); (2) exposure to LDA (i.e., low-dose aspirin as antithrombotic agent; ATC: B01AC06); and (3) their combinations.

2.4. Patient covariates

For each reports, information on the presence of comorbidity, or concomitant use of other drugs, previously identified as risk factor for GI disease (i.e., antineoplastic agents, drugs for cardiovascular diseases, drug for nervous system, corticosteroids, acid/related disorder agents, other antithrombotic agents, with exception of low-dose aspirin) were also retrieved, whenever available.

Table 1
Characteristics of GI cases and non-GI cases included in the ADR spontaneous reporting.

	All cases *N* = 2804 (100%)	GI Cases *N* = 374 (13.3%)	Non-GI cases *N* = 2430 (86.7%)	*P* value
Sex				<0.001
Women	1511 (53.9)	140 (37.4)	1371 (56.4)	
Men	1293 (46.1)	234 (62.6)	1059 (43.6)	
Mean age (±SD)	57.2 (15.8)	64.7 (13.9)	56.0 (15.8)	<0.001
Seriousness of adverse event				<0.001
No serious	1375 (49.0)	15 (4.0)	1360 (56.0)	
Serious	1397 (49.8)	359 (96.0)	1038 (42.7)	
NA	32 (1.1)	0	32 (1.3)	
Type of seriousness (% of serious events)				<0.001
Hospitalization	835 (59.8)	354 (98.6)	481 (46.3)	
Other conditions	388 (27.8)	3 (0.8)	385 (37.1)	
Life-threatening	112 (8.0)	2 (0.6)	110 (10.6)	
Death	37 (2.6)	–	37 (3.6)	
Invalidity	24 (1.7)	–	24 (2.3)	
Congenital anomalies	1 (0.1)	–	1 (0.1)	
Outcome				<0.001
Getting better	1102 (39.3)	331 (88.5)	771 (31.7)	
Fully recovered	1006 (35.9)	19 (5.1)	987 (40.6)	
Not available	465 (16.6)	21 (5.6)	444 (18.3)	
Side effect continuing	144 (5.1)	3 (0.8)	141 (5.8)	
Caused death	45 (1.6)	–	45 (1.9)	
Recovered with some lasting effects	42 (1.5)	–	42 (1.7)	
Type of reporter				<0.001
Hospital physician	1809 (64.5)	331 (88.5)	1478 (60.8)	
Pharmacist	457 (16.3)	30 (8.0)	427 (17.6)	
Specialist	178 (6.3)	6 (1.6)	172 (7.1)	
General practitioner	171 (6.1)	6 (1.6)	165 (6.8)	
Other	189 (6.7)	1 (0.3)	188 (7.7)	
Pre-existing condition	166 (5.9)	48 (12.8)	118 (4.9)	<0.001

Database from Campania region, southern Italy.

2.5. Data-analysis

First, a descriptive analysis of reports of GI events and of non-GI events included in RNF from Campania region for the period of interest was performed (i.e., total number of reports and other demographic information, including age and gender, reporter type, concomitant medications, comorbidities, type of GI events).

Second, suspected ADR reporting odds ratio (ROR) with 95% confidence intervals was calculated as measure of disproportionality to evaluate the association with GI events [26]. We compared the crude reporting odds of exposure to each group of drugs in GI cases with the odds of exposure to the same group of drugs in all non-GI ADR reports. By using multivariate conditional logistic regression analysis, crude RORs were adjusted for all covariates which changed the point estimate of the association between each group of drugs and GI events by more than 10%: age, and concomitant use of antineoplastic agents or drugs for cardiovascular diseases. Third, we analyzed the associations with GI events for each individual NSAID involved in at least 3 reports of GI events compared to all other reports from the other drugs. In order to investigate the effect of a specific NSAID and to limit confounding by indication, a sensitivity analysis by restricting to the drugs belonging to the same therapeutic class (i.e. NSAIDs) was performed. As the last step, we investigated the effect modification by sex, and concomitant use of specific drug classes, such as proton pump inhibitors, corticosteroids or other antithrombotic agents, by stratifying the analysis according to these specific covariates [13]. The statistical package SPSS (version 21) was used for all statistical analyses.

3. Results

In the period 2007–2011, RNF database collected 2816 suspected ADR reports in the population aged >18 years of Campania region. After exclusion of 12 reports of ADRs related to heartburn without any other symptom/sign, 2804 ADR reports remained and were analyzed. Among them, 374 (13.3%) reports concerned GI ADRs and 2430 (86.7%) refer to other ADRs. Main characteristics significantly differed between ADRs of interest and the other ADRs, as described in Table 1. The majority of GI ADRs were reported in men (*n* = 234, 62.6%), while the other ADRs were more frequent in women (*n* = 1371, 56.4%). GI ADRs occurred in older people and were more serious than the other ADRs (mean age: 64.7 vs. 56.0 and seriousness: 96.0% vs. 42.7%, respectively). In terms of the type of severity, almost all serious GI ADRs (*n* = 354, 98.6%) required a hospital admission or hospitalization prolonged, but the majority of them got better (*n* = 331, 88.5%) or fully resolved (*n* = 19, 5.1%). Overall, ADR reports were mostly issued by hospital physician (*n* = 1,809; 64.5%), followed by pharmacist (*n* = 457; 16.3%), regardless of the type of ADRs, but the proportion of the type of reporter was heterogeneously distributed among GI ADRs and other ADRs. Actually, the frequency of reports issued by hospital physician was higher for GI ADRs than other ADRs (88.5% vs. 60.8%, respectively), while the opposite trend was observed for pharmacists (8.0% to 17.6%), specialist (1.6% vs. 7.1%), and general practitioner (1.6% vs. 6.8%). Around 90% of the GI ADRs occurred in patients exposed to other non-suspected drugs (data not shown). In detail, the most frequent concomitant drugs were antineoplastic agents, cardiovascular therapy, CNS drugs, corticosteroids and acid-related disorder therapy (Table 2). Among the type of GI events, we found that GI bleeding was reported in the highest number of cases (349, 42.3%), followed by gastric ulceration (163, 19,8%), and duodenal ulceration (151, 18.3%) (Table 3). Overall, upper GI bleeding was the most frequently reported event compared to the lower one (upper GI bleeding = 88%; lower GI bleeding = 12%) (Table 3).

Ranked by the absolute number of GI reports, the highest number of GI events were reported for LDA use (no. of cases = 107,

Table 2
Concomitant therapies previously identified as potential risk factors.[a]

DRUGs	All cases*N* = 2804 (%)	GI cases*N* = 374 (%)	Non-GI cases*N* = 2430 (%)
Antineoplastics	1273 (45.4)	15 (4.0)	1258 (51.8)
Anti-hypertensive	616 (22.0)	225 (60.2)	391 (16.1)
Acid related disorders (PPIs)	368 (13.1)	66 (17.7)	302 (12.4)
Corticosteroids	278(9.9)	10 (2.7)	268 (11.0)
Other anti-thrombotics	180 (6.4)	41 (10.7)	139 (5.7)
Antidepressants	70 (2.5)	9 (2.4)	61 (2.5)

The Table includes only concomitant therapies as previously defined as potential risk factors for GI complications, thus the sum of the column does not correspond to the overall total number of cases.

[a] The distribution is not mutually exclusive.

Table 3
Distribution of different GI events among GI cases.

GI events	*N* (%)
Gastrointestinal bleeding	349 (42.3)
Upper GI bleeding	307 (88)
Lower GI bleeding	42 (12)
Gastric ulceration	163 (19.8)
Duodenal ulceration	151 (18.3)
Gastritis (and/or no erosive)	109 (13.2)
Duodenitis (and/or no erosive)	43 (5.2)
Oesophagitis (and/or no erosive)	10 (1.2)
All events[a]	825 (100)

[a] The total number of events exceed the total number of GI cases (*N* = 374), because a single report might include more than one events.

39.6%), followed by combined use of LDA and other NSAIDs (no. of cases = 92, 34.1%), the multiple NSAIDs use (no. of cases = 82, 30.4%) and for any NSAIDs used alone (no. of cases = 73, 27.0%). Disproportionality analysis showed that either LDA, alone or in combination with NSAIDs, or NSAIDs, alone or in combination, were significantly associated with the occurrence of GI events compared to all other reports (Table 4). However, ranked by the strength of the adjusted RORs, the combination of different NSAIDs showed the highest association, followed by the combination LDA/NSAIDs, the use of NSAIDs as monotherapy and the use of LDA alone, with the lowest association (Table 4). Looking at individual NSAIDs involved in at least three GI reports, the highest association with GI events was observed for reports related to ketorolac exposure (no. of cases = 45; adj. ROR 28.5, 95% CI: 13.1–62.1), nimesulide (no. of cases = 96; adj. ROR 24.8, 15.1–40.7), diclofenac (no. of cases = 64; adj. ROR 22.4, 95% CI: 11.9–42.2), aspirin (no. of cases = 42; adj. ROR 14.7, 95% CI: 8.0–27.0), ketoprofen (no. of cases = 49; adj. ROR 9.1, 95% CI: 5.3–15.4), and ibuprofen (no. of cases = 13; adj. ROR 7.8, 95% CI: 3.2–18.6) (Table 5). When restricting the analysis to the drugs belonging to the same therapeutic class (i.e. NSAIDs), for most NSAIDs RORs decreased but remained still significant, pointing to confounding by indication or class effects, while no significant association was observed for ibuprofen and ketoprofen (Table 6). To inspect effect modification by sex, sex-specific RORs were calculated for all drugs of interest. Although the highest number of GI cases was reported in men, there were mild or null differences among sex in the associations for the most of drugs, with some exceptions. Actually, a trend toward an increase in strength of ROR was observed in women for aspirin (ROR 35.2: 13.0-95.4, in women vs. ROR 8.0: 3.7–17.4, in men) and ketorolac (ROR 51.0: 15.1–172.0, in women vs. ROR 18.7: 6.7–51.9, in men) (Table 7). Due to the low number of reports including concomitant use of those specific drug classes, only sex-specific RORs were assessed.

4. Discussion

We aimed to investigate the associations between GI complications and use of NSAIDs or LDA, as monotherapy or in combination, from the spontaneous ADR reporting system in Campania region from 2007 to 2011. Moreover, we attempted to estimate the association between GI events and each individual NSAID. To the best of our knowledge, this is the first study providing data on the GI safety profile of the individual NSAIDs or combination between them or with LDA in real-life conditions in Southern Italy, based on spontaneous reporting system.

Data from the descriptive analysis showed that, although overall ADRs mostly occurred in female population, as previously reported [27], and in people younger than 60, the majority of GI ADRs occurred in men aged 65 years, treated with more than one drug besides those of interest, especially anti-hypertensive and other anti-thrombotics. Moreover, in line with the analyses from other national pharmacovigilance systems [28,29], our results showed that the most of selected GI cases was serious and required hospitalization. Upper GI complications, especially upper GI bleeding, were the most frequently reported type of events. This is consistent with previous reports. Specifically, Lanas et al. showed that hospital admission due to upper GI complications were six times more frequent than the lower [30]; moreover, through a population-based study evaluating the features of hospitalizations related to GI events, was observed that male gender and NSAID use were associated to a greater extent with upper GI events [31]. From disproportionality analysis, as expected, either LDA, alone or in combination with NSAIDs, or NSAIDs, as monotherapy or combined regimen, were significantly associated with the occurrence of GI events compared to all other reports. Specifically the highest associations were found for the combined use of NSAIDs and/or LDA, whilst the lowest associations were for their respective monotherapy. Baseline characteristics of the selected population, even if extracted from ADR reports from the Campania region, are similar to those reported in prior observational studies conducted with different methodological approaches with the aim to analyze risk of GI complications induced by NSAIDs or LDA use [7,8,14,32–34]. Specifically, it has well been demonstrated that features such as older age (>60 years), male gender, cardiovascular diseases and treatment with antithrombotic drugs play an important role as potential risk factors of developing GI complication during NSAID exposure (LDA included) [35–38]. The present study also confirms previous results demonstrating the associations between both NSAID and LDA exposure and GI complications. Moreover, we also found an higher positive association for NSAID monotherapy than for LDA alone, in accordance with previous studies estimating the risk of upper or lower GI complications of NSAIDs, LDA and their combinations [13–15]. With regard to combined therapy, our analysis shows that association of multiple NSAIDs have the highest reporting odds ratio. To this, although several data are available on the risk of GI events associated with the use of NSAIDs and LDA as monotherapy or their combination, on the other hand only few studies to date analyzed the associations with multiple NSAIDs use. In support to this result, in a case-control study assessing the association between upper gastrointestinal bleeding (UGIB) and NSAIDs, de Abajo et al. highlighted a greater UGIB risk among users of more than one NSAID [9]. Moreover, a review of published epidemiolog-

Table 4
RORs of GI event reports related to NSAIDs and LDA compared to all other ADR reports.

	GI cases 374 (%)	Non-GI cases 2430 (%)	ROR (95%CI)	Adj[a] ROR (95%CI)
LDA[$]	107 (39.6)	141 (5.8)	79.0 (47.6–131.2)	28.7 (16.5–49.9)
LDA[b]/NSAIDs	92 (34.1)	10 (0.4)	958.2 (436.0–2105.5)	343.6 (148.1–797.4)
NSAIDs combination (2 or more)	82 (30.4)	18 (0.7)	474.5 (241.8–930.9)	510.1 (237.4–1096.0)
Any NSAID	73 (27.0)	178 (7.3)	42.7 (25.4–71.7)	46.3 (26.2–81.7)
Other medications	20 (7.4)	2083 (85.7)	ref	

[a] Adjusted RORs for age, and concomitant use of antineoplastics and cardiovascular agents.
[b] Low-dose-aspirin.

Table 5
RORs for GI events of individual NSAID[a] compared to the reports from all other drugs.

	GI cases*N* = 374 (%)	Non-GI cases*N* = 2430 (%)	ROR (95%CI)	Adj[b] ROR (95%CI)
Ketorolac	45(12.0)	9 (0.4)	36.8 (17.8–76.0)	28.5 (13.1–62.1)
Nimesulide	96 (25.7)	31 (1.3)	26.7 (17.5–40.8)	24.8 (15.1–40.7)
Diclofenac	64 (17.1)	20 (0.8)	24.9 (14.9–41.7)	22.4 (11.9–42.2)
Aspirin	42 (11.2)	20 (0.8)	15.2 (8.8–26.3)	14.7 (8.0–27.0)
Ketoprofen	49 (13.1)	34 (1.4)	10.6 (6.8–16.7)	9.1 (5.3–15.4)
Ibuprofen	13 (3.5)	14 (0.6)	6.2 (2.9–13.3)	7.8 (3.2–18.6)

[a] Only individual NSAIDs involved in at least three GI reports have been included in the Table.
[b] Adjusted for age, and concomitant use of antineoplastics and cardiovascular agents.

Table 6
RORs for GI events of individual NSAID[a] within the therapeutic class (i.e. only NSAIDs).

	GI cases*N* = 155 (%)	Non-GI cases*N* = 188 (%)	ROR (95%CI)	Adj[b]ROR (95%CI)
Ketorolac	31 (20.0)	8 (4.3)	5.6 (2.5–12.7)	4.7 (2.0–11.1)
Nimesulide	66 (42.6)	30(16.0)	3.9 (2.3–6.5)	3.7 (2.1–6.6)
Diclofenac	43 (27.7)	19 (10.1)	3.4 (1.9–6.2)	3.8 (1.8–7.9)
Aspirin	35 (22.6)	19 (10.1)	2.6 (1.4–4.7)	2.3 (1.2–4.6)
Ketoprofen	31 (20.0)	32 (17.0)	1.2 (0.7–2.1)	1.3 (0.7–2.3)
Ibuprofen	13 (8.4)	14 (7.4)	0.9 (0.4–2.2)	1.3 (0.5–3.6)

[a] Only individual NSAIDs involved in at least three GI reports have been included in the Table.
[b] Adjusted for age, and concomitant use of antineoplastics and cardiovascular agents.

Table 7
RORs for GI events[a] associated to individual NSAID or LDA stratified by sex.

	Women (No. of reports = 1511)			Men (No. of reports = 1293)		
	GI cases*N* = 140	Non-GI cases*N* = 1371	Adj. ROR[b]	GI cases*N* = 234	Non-GI cases*N* = 1059	Adj. ROR[b]
Ketorolac	19 (13.6)	4 (0.3)	51.0 (15.1–172.0)	26 (11.1)	5 (0.5)	18.7 (6.7–51.9)
Nimesulide	34 (24.3)	20 (1.5)	27.6 (13.3–57.2)	62 (26.5)	11 (1.0)	27.3 (13.0–57.6)
Diclofenac	24 (17.1)	12 (0.9)	21.7 (8.4–56.5)	40 (17.1)	8 (0.8)	22.5 (9.3–54.6)
Aspirin	18 (12.9)	8 (0.6)	35.2 (13.0–95.4)	24 (10.3)	12 (1.1)	8.0(3.7–17.4)
Ketoprofen	18 (12.9)	23 (1.7)	9.2 (4.2–20.3)	31 (13.3)	11 (1.0)	10.5 (4.8–23.0)
Ibuprofen	6 (4.3)	8 (0.6)	7.3 (2.1–25.9)	7 (3.0)	6 (0.6)	9.0 (2.6–30.6)
LDA[c]	70 (50.0)	80 (5.8)	5.8 (3.5–9.5)	129 (55.1)	71 (6.7)	7.1 (4.6–10.9)

[a] Only individual NSAIDs involved in at least three GI reports have been included in the Table.
[b] Adjusted for age and concomitant use of antineoplastics and cardiovascular agents.
[c] Low-dose-aspirin.

ical data on the effect of multiple use of NSAIDs on the risk of upper GI complications (UGIC), showed that combined regimen of NSAIDs had about 10 times increased risk of developing UGIC compared with non users (RR 18.0; CI 95% 9.0–36.1), while the combination LDA/NSAIDs was associated with a relative risk slightly higher than the sum of their individual risks (RR 8.2; CI95% 5.3–12.8) [15]. As mentioned before, several risk factors for NSAID-induced GI damage have been identified, but besides these, others such as multiple NSAIDs use, high dose and long-term therapy also act increasing the risk of GI complication among NSAIDs users [39]. Furthermore, the high percentage of multiple NSAIDs reports observed in our data-set, 30.4% of the GI cases, offers us the opportunity to make some comments. We could only speculate, but not rule out, since the nature of this analysis, that multiple NSAIDs use reported could be partly due to the combination of doctor prescriptions and over-the-counter (OTC) use of NSAIDs. In fact, NSAIDs are nowadays freely available as OTC drugs in many countries and their use seems to be widespread, accounting for 10–40% among elderly people [40]. However, even if the total dosage in the OTC packages is lower than the amount in the prescribed packages, the combined regimen of two or more NSAIDs, especially among high GI risk patients, deserves some concerns. Unfortunately, this inappropriate use is very common, with 38% of patients using NSAIDs as prescribed and OTC at the same time, and 26% of OTC users and 8% of prescription users taking higher dose than recommended [41]. Confirming these data, more recently, Cavagna et al. evaluating the NSAIDs pattern consumption among osteoarthritis and rheumatoid arthritis patients has revealed that NSAID overuse, which comprises both prescription and OTC drugs additionally taken, was very common among both patient group (39.5% for rheumatoid arthritis patients and 47% for osteoarthritis patients) [42].

Looking at individual NSAIDs, we found that the highest association with GI ADRs was observed for ketorolac use followed by nimesulide, diclofenac, aspirin, ketoprofen, and ibuprofen. Moreover this scenario remained unchanged even after restricting the analysis to the drugs belonging to the same therapeutic class, except for ibuprofen and ketoprofen for which no significant associations were found, probably due to both uncontrolled confounding by indication and/or severity of disease and pharmacokinetics/pharmacodynamics differences between NSAIDs. First of all, in accordance with previous studies [2,5,6] we found variability among associations between each NSAID and GI complication. This variability is based on two main factors such as COX-1/COX-2 selectivity, plasma half-life and type of formulations [1]. These characteristics, taken together with dose, duration of exposure and patients clinical features, could partly explain the differences between NSAIDs found in our analysis. In fact, it has been well demonstrated that NSAIDs with long plasma half-life had a greater risk of GI complication [1,2,5,6] and according to this evidence, our results showed the highest positive association for ketorolac and the lowest one for ibuprofen followed by ketoprofen. The high association found for diclofenac is in apparent contrast with the relationship between long plasma half-life and increase of the GI risk. In fact, diclofenac, together with ibuprofen and ketoprofen, has a short plasma half-life that should give it a better GI tolerability; however, inappropriate use of this NSAID in terms of dose and/or duration of exposure (but also of ibuprofen and ketoprofen) could neutralize this positive characteristic [1] and thus explain our results. However, we can only speculate on the inappropriate use of diclofenac because we are unable to take into account either dose and duration of exposure, since they are not always reported in ADR reports. However, in a retrospective study assessing the pattern of use of NSAIDs and opioids in a Italian population, Ussai et al. have recently highlighted that inappropriate use of NSAIDs (that is duration of use >21 consecutive days) is still widespread and amounts to over 97% of the study population [43]. On the other hand, we can not rule out that uncontrolled factors may have affect our analysis. Similar to diclofenac, nimesulide also showed a high positive association with GI complication despite its pharmacodynamic properties and to recent data. Specifically, nimesulide is characterized by an intermediate COX-2 selectivity and thus has a greater potential for sparing COX-1 activity than non-selective NSAIDs [1]. Moreover, as demonstrated by Castellsague et al. [44], nimesulide, the most widely used NSAID in Italy, was in the low-medium range of relative risk of GI complication compared with other NSAIDs, although the authors assert that the low RR may be due to lack of information on the use of OTC drugs, given the fact that in Italy it has been estimated that about 50% of NSAIDs prescriptions, especially for acute and off-label indications, are not reimbursed. Again, we can only speculate that inappropriate use, in terms of indication, dose or duration of exposure, together with uncontrolled bias could explain our results. The present study suffers from several limitations, which mostly affect studies based on case/non-case methodology within a spontaneous reporting system such as the underreporting of ADRs. Moreover, we cannot rule out an association bias rather than a recall bias taking in to account the well-known health professional's low attitude to reporting mostly severe ADRs. Moreover, although we attempted to control for age and concomitant therapy (antineoplastic and drugs for cardiovascular diseases), we were unable to account for some potentially important factors, which could explain our results in apparent contrast to what it has been largely reported, such as dose, duration of exposure, prescription or OTC drugs, since they are not always exhaustively reported in spontaneous reporting system. Finally, another limitation of the present study is the inability of matching our data with those of prescription which could justify the differences between our results and those showed in other studies carried out with both different and similar methodology. However, despite the limitations described above, strengths of the present study are that data based on spontaneous reporting system give the opportunity of observe the real-life drug use and their actual safety profiles. Moreover, the causality assessment for each adverse event–drug pair was made by GI clinicians. Noteworthy, spontaneous reporting system might be a tool to evidence the inappropriate drug use patterns. As far as we know, this is the first study providing data on the GI safety profile of some individual NSAIDs or combination between them or with LDA under their real conditions of use in southern Italy (Campania region) based on spontaneous reporting system.

5. Conclusions

In conclusion, the present study describes the highest positive association between multiple NSAIDs use, followed by LDA/NSAIDs combination. Looking at individual NSAID, in line with previous studies, we found the highest association between ketorolac use and GI complications while the lowest with ibuprofen and ketoprofen. However, the high associations found for diclofenac and nimesulide, in contrast with previous data, deserve further investigations to be confuted or confirmed. Our data highlight once again the primary role of the national spontaneous reporting system to bring out potential signals [45–54] which, however, have to be furtherly studied in-depth with ad hoc population-based studies and matched with prescription and/or use data.

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